

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1 (Previously Presented). A bacteriochlorophyll derivative containing at least one, preferably two or three, negatively charged groups or acidic groups that are converted to negatively charged groups at the physiological pH, or both, excluding pentacyclic bacteriochlorophyll derivatives having a free $\text{CH}_2\text{CH}_2\text{COOH}$ or a $\text{CH}_2\text{CH}_2\text{COO}^-$ group at position 17, and tetracyclic bacteriochlorophyll derivatives devoid of a central metal atom and having a $-\text{CH}_2\text{CH}_2\text{COOH}$ group at position 17, a $-\text{CH}_2\text{COOH}$ or $-\text{COOH}$ group at position 15, a $-\text{COOH}$ group at position 13, methyl groups at the positions 2, 7, 12, 18, and ethyl groups at the positions 3 and 8.

2 (Original). A bacteriochlorophyll derivative according to claim 1 containing two negatively charged groups.

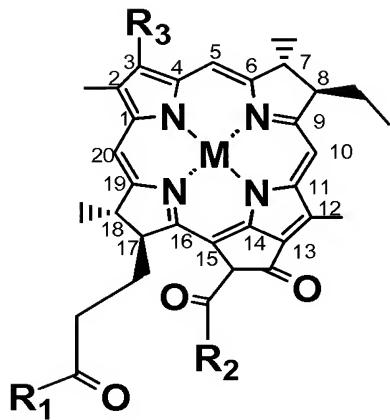
3 (Withdrawn). A bacteriochlorophyll derivative according to claim 1 containing three negatively charged groups.

4 (Previously Presented). A bacteriochlorophyll derivative according to claim 1 wherein said at least one negatively charged group is selected from the group consisting of COO^- , COS^- , SO_3^- , and PO_3^{2-} .

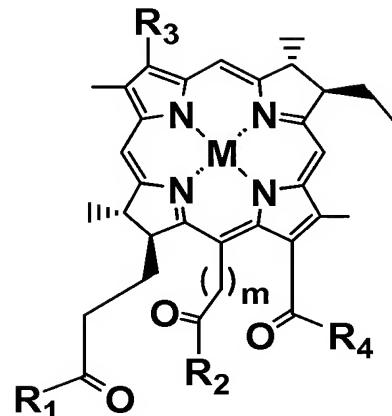
5 (Withdrawn). A bacteriochlorophyll derivative according to claim 1 wherein said at least one acidic group that is converted to a negatively charged group at the physiological pH is selected from the group consisting of COOH , COSH , SO_3H , and PO_3H_2 .

6 (Previously Presented). A bacteriochlorophyll derivative according to claims 1 derived from a natural or synthetic derivative of bacteriochlorophyll, including compounds in which the central Mg atom has been deleted or replaced by other metal atoms.

7 (Previously Presented). A bacteriochlorophyll derivative according to claim 1 of the formula I or II:



(I)



(II)

wherein

M represents 2H or a metal atom selected from the group consisting of divalent Pd, Pt, Co, Sn, Ni, Cu, Zn and Mn, and trivalent Fe, Mn and Cr;

R₁, R₂, and R₄ each independently is Y- R₅;

Y is O, S or -NR₆;

R₃ is selected from the group consisting of -CH=CH₂, -C(=O)-CH₃, -C(=O)-H, -CH=NR₇, -C(CH₃)=NR₇, -CH₂-OR₇, -CH₂-SR₇, -CH₂-NR₇R'₇, -CH(CH₃)-OR₇, -CH(CH₃)-SR₇, -CH(CH₃)-NR₇R'₇, -CH(CH₃)-Hal, -CH₂-Hal, -CH₂-R₇, -CH=CR₇R'₇, -C(CH₃)=CR₇R'₇, -CH=CR₇Hal, -C(CH₃)=CR₇Hal, and -C≡CR₇;

R₅, R₆, R₇ and R'₇ each independently is H or selected from the group consisting of:

(a) C₁-C₂₅ hydrocarbyl optionally containing one or more heteroatoms, carbocyclic or heterocyclic moieties, and/or

optionally substituted by one or more functional groups selected from the group consisting of halogen, oxo, OH, SH, CHO, NH₂, CONH₂, a negatively charged group, and an acidic group that is converted to a negatively charged group at the physiological pH;

- (b) a residue of an amino acid, a peptide or of a protein; and
- (c) when Y is O or S, R₅ may further be R₈⁺;

m is 0 or 1; and

R₈⁺ is H⁺ or a cation;

provided that:

(i) at least one, preferably two, of R₅, R₆, R₇ and R'₇ is a hydrocarbon chain as defined in (a) above substituted by a negatively charged group or by an acidic group that is converted to a negatively charged group at the physiological pH ; or

(ii) at least one, preferably two, of R₁, R₂, and R₄ is OH, SH, O⁻R₈⁺ or S⁻R₈⁺; or

(iii) at least one of R₁, R₂, and R₄ is OH, SH, O⁻R₈⁺ or S⁻R₈⁺ and at least one of R₅, R₆, R₇ and R'₇ is a hydrocarbon chain substituted by a negatively charged group or by an acidic group that is converted to a negatively charged group at the physiological pH; or

(iv) at least one of R_1 , R_2 , and R_4 is OH, SH, $O^- R_8^+$ or $S^- R_8^+$ and at least one of R_5 , R_6 , R_7 and R'_7 is a residue of an amino acid, a peptide or of a protein; or

(v) at least one of R_5 , R_6 , R_7 and R'_7 is a hydrocarbon chain substituted by a negatively charged group or by an acidic group that is converted to a negatively charged group at the physiological pH and at least one of R_5 , R_6 , R_7 and R'_7 is a residue of an amino acid, a peptide or of a protein;

but excluding the compounds of formula I wherein M is as defined, R_3 is $-C(=O)CH_3$, R_1 is OH or OR_8^+ and R_2 is $-OCH_3$, and the compound of formula II wherein M is 2H, R_3 is $-C(=O)CH_3$, R_1 , R_2 and R_4 are OH, and m is 0 or 1.

8 (Previously Presented). A bacteriochlorophyll derivative of the formula I or II according to claim 7 wherein said negatively charged groups are selected from the group consisting of COO^- , COS^- , SO_3^- , and PO_3^{2-} .

9 (Withdrawn). A bacteriochlorophyll derivative of the formula I or II according to claim 7 wherein said acidic groups that are converted to negatively charged groups at the physiological pH are selected from the group consisting of $COOH$, $COSH$, SO_3H , and PO_3H_2 .

10 (Withdrawn). A bacteriochlorophyll derivative of the formula I or II according to claim 7 wherein R₁ is Y- R₅; Y is O, S or NH; and R₅ is a hydrocarbon chain substituted by functional groups selected from of the group consisting of OH, SH, SO₃H, NH₂, CONH₂, COOH, COSH, and PO₃H₂.

11 (Withdrawn). A bacteriochlorophyll derivative of the formula I or II according to claim 7 wherein R₅ is the residue of an amino acid, a peptide or a protein.

12 (Previously Presented). A bacteriochlorophyll derivative of the formula I or II according to claim 7 containing a central Pd metal atom.

13 (Withdrawn). A bacteriochlorophyll derivative of the formula I according to claim 7 wherein:

M is Pd;

R₁ is -NH- (CH₂)_n-SO₃⁻R₈⁺, -NH- (CH₂)_n-COO⁻R₈⁺; -NH- (CH₂)_n-PO₃²⁻ (R₈⁺)₂ ;

R₂ is methoxy;

R₃ is -C(=O)-CH₃;

R₈⁺ is a monovalent cation such as K⁺, Na⁺, Li⁺, NH₄⁺; and n is an integer from 1 to 10, preferably 2 or 3.

14 (Previously Presented). A bacteriochlorophyll derivative of the formula II according to claim 7 wherein:

M represents 2H, divalent Pd, Cu, or Zn or trivalent Mn;

R₁ is -O⁻R₈⁺, -NH-(CH₂)_n-SO₃⁻R₈⁺, -NH-(CH₂)_n-COO⁻R₈⁺ or -NH-(CH₂)_n-PO₃²⁻(R₈⁺)₂; or Y-R₅ wherein Y is O, S or NH and R₅ is the residue of an amino acid, a peptide or a protein;

R₂ is C₁-C₆ alkoxy, preferably methoxy;

R₃ is -C(=O)-CH₃, -CH=N-(CH₂)_n-SO₃⁻R₈⁺; -CH=N-(CH₂)_n-COO⁻R₈⁺; -CH=N-(CH₂)_n-PO₃²⁻(R₈⁺)₂; -CH₂-NH-(CH₂)_n-SO₃⁻R₈⁺; -CH₂-NH-(CH₂)_n-COO⁻R₈⁺; or -CH₂-NH-(CH₂)_n-PO₃²⁻(R₈⁺)₂;

R₄ is -NH-(CH₂)_n-SO₃⁻R₈⁺; -NH-(CH₂)_n-COO⁻R₈⁺; or -NH-(CH₂)_n-PO₃²⁻(R₈⁺)₂;

R₈⁺ is a monovalent cation, preferably K⁺; and

m is 1, and n is an integer from 1 to 10, preferably 2 or 3.

15 (Previously Presented). A bacteriochlorophyll derivative of formula II in claim 7 wherein:

M is divalent Pd;

R₁ is -O⁻R₈⁺, -NH-(CH₂)_n-SO₃⁻R₈⁺, or Y-R₅ wherein Y is O, S or NH and R₅ is the residue of an amino acid, a peptide or a protein;

R₂ is C₁-C₆ alkoxy, preferably methoxy;

R₃ is -C(=O)-CH₃, -CH= N-(CH₂)_n-SO₃⁻ R₈⁺; or -CH₂-NH-(CH₂)_n-SO₃⁻ R₈⁺;

R₄ is -NH-(CH₂)_n-SO₃⁻ R₈⁺; NH-(CH₂)_n-COO⁻ R₈⁺; or NH-(CH₂)_n-PO₃²⁻ (R₈⁺)₂;

R₈⁺ is a monovalent cation, preferably K⁺;

m is 1, and n is 2 or 3.

16 (Withdrawn). A bacteriochlorophyll derivative of the formula I according to claim 13, consisting of the compound Palladium bacteriopheophorbide a 17³-(3-sulfopropyl)amide potassium salt.

17 (Previously Presented). A bacteriochlorophyll derivative of the formula II according to claim 15, selected from the group consisting of:

Palladium 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹-(2-sulfoethyl) amide dipotassium salt;

3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹-(2-sulfoethyl) amide dipotassium salt;

Palladium 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹,17³-di(3-sulfopropyl)amide dipotassium salt;

Palladium 3¹-(3-sulfopropylimino)-15-methoxycarbonylmethyl-rhodobacterio-chlorin 13¹,17³-di(3-sulfopropyl)amide tripotassium salt;

Copper (II) 3^1 -oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin
 13^1 -(2-sulfoethyl) amide dipotassium salt;
Zinc 3^1 -oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1 -(2-sulfoethyl) amide dipotassium salt;
Manganese (III) 3^1 -oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1 -(2-sulfoethyl) amide dipotassium salt;
Palladium 3^1 -oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin
 13^1 -(2-sulfoethyl) amide, 17^3 -(N-immunoglobulin G) amide
potassium salt;
Palladium 3^1 -oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin
 13^1 -(2-carboxy-ethyl) amide dipotassium salt;
Palladium 3^1 -oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin
 13^1 -(3-phosphopropyl) amide tripotassium salt; and
Palladium 3^1 -(3-sulfopropylamino)-15-methoxycarbonylmethyl-
rhodobacteriochlorin $13^1, 17^3$ -di(3-sulfopropyl) amide
tripotassium salt.

18 (Original). Palladium 3^1 -oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1 -(2-sulfoethyl) amide dipotassium salt.

19 (Previously Presented). A pharmaceutical composition comprising a bacteriochlorophyll derivative

according to claims 1, and a pharmaceutically acceptable carrier.

20 (Original). The pharmaceutical composition according to claim 19 for photodynamic therapy.

21 (Original). The pharmaceutical composition according to claim 20 for vascular-targeting photodynamic therapy.

22 (Previously Presented). The pharmaceutical composition according to claim 20 for photodynamic therapy of tumors, including metastatic tumors.

23 (Original). The pharmaceutical composition according to claim 22 for photodynamic therapy of melanoma, colon, breast, lung, or prostate cancer.

24 (Previously Presented). The pharmaceutical composition according to claim 20 for photodynamic therapy of age-related macular degeneration.

25 (Previously Presented). The pharmaceutical composition according to claim 20 for photodynamic therapy of benign prostate hypertrophy.

26 (Original). The pharmaceutical composition according to claim 19 for tumor diagnosis.

27 (Original). A pharmaceutical composition according to claim 19 for killing cells or infectious agents comprising bacteria and viruses.

28 (Original). The pharmaceutical composition according to claim 27 for *in vitro* killing of cells or infectious agents comprising bacteria and viruses in a biological product upon illumination of said product.

29 (Original). The pharmaceutical composition according to claim 28 wherein said biological product is blood.

30-35 (Cancelled).

36 (Withdrawn). A method for tumor photodynamic therapy which comprises:

(a) administering to an individual in need a compound according to claims 1; and
(b) irradiating the local of the tumor.

37 (Withdrawn). A method for photodynamic therapy of age-related macular degeneration which comprises: (a) administering to an individual in need a compound according to claims 1; and (b) irradiating the local of the macular degeneration.

38 (Withdrawn). A method for tumor diagnosis which comprises:

(a) administering to a subject suspected of having a tumor, a compound according to claim 1; and
(b) irradiating the subject by standard procedures and measuring the fluorescence of the suspected area, wherein a higher fluorescence indicates tumor sites.

39 (Withdrawn). In a method for photodynamic therapy using a photosensitizer, the improvement wherein said photosensitizer is a bacteriochlorophyll derivative according to claim 1.

40 (Withdrawn). In a method for diagnosis of tumors using a photosensitizer, the improvement wherein said photosensitizer is a bacteriochlorophyll derivative according to claims 1.

41 (Withdrawn). In an in vitro method for killing of cells or infectious agents comprising bacteria and viruses, using a photosensitizer, the improvement wherein said photosensitizer is a bacteriochlorophyll derivative according to claim 1.

42 (Withdrawn). The compound Palladium bacteriopheophorbide a 17^3 -(3-sulfo-1-oxysuccinimide) ester sodium salt, as an intermediate.

43 (Withdrawn). A method for the preparation of compounds of formula II In claim 7 wherein R_1 is $-O^- R_8^+$; R_2 is $-OCH_3$; R_3 is acetyl; R_4 is a group $-NH-(CH_2)_n-SO_3^- R_8^+$; R_8^+ is a monovalent cation; m is 1 and n is 1 to 10, which comprises:
(i) reacting the corresponding M-bacteriopheophorbide of formula I wherein R_1 is OH with an aminosulfonic acid of the formula $H_2N-(CH_2)_n-SO_3H$ in a R_8^+ -buffer; and
(ii) isolating the desired compound of formula II.

44 (Withdrawn). The method according to claim 43 for preparation of palladium 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹-(2-sulfoethyl) amide dipotassium salt which comprises: (i) reacting Pd-bacteriopheophorbide a with taurine of the formula H₂N-(CH₂)₂-SO₃H in a K⁺-buffer; and (ii) isolating the title compound.

45 (Withdrawn). A method for the preparation of compounds of formula II in claim 7 wherein R₁ is -O⁻R₈⁺; R₂ is -OCH₃; R₃ is acetyl; R₄ is a group -NH-(CH₂)_n-COO⁻R₈⁺; R₈⁺ is a monovalent cation; m is 1 and n is 1 to 10, which comprises: (i) reacting the corresponding M-bacteriopheophorbide of formula I wherein R₁ is OH with an aminocarboxylic acid of the formula H₂N-(CH₂)_n-COOH in a R₈⁺-buffer; and (ii) isolating the desired compound of formula II.

46 (Withdrawn). A method for the preparation of compounds of formula II in claim 7 wherein R₁ is -O⁻R₈⁺; R₂ is -OCH₃; R₃ is acetyl; R₄ is a group -NH-(CH₂)_n-PO₃²⁻(R₈⁺)₂; R₈⁺ is a monovalent cation; m is 1 and n is 1 to 10, which comprises: (i) reacting the corresponding M-bacteriopheophorbide of formula I wherein R₁ is OH with an aminophosphonic acid of the formula H₂N-(CH₂)_n-PO₃H₂ in a R₈⁺-buffer; and (ii) isolating the desired compound of formula II.

47 (Withdrawn). A method for the preparation of compounds of formula II in claim 7 wherein R₁ and R₄ contain the same negatively charged group, which comprises:

- (i) reacting the corresponding M-bacteriopheophorbide with an excess of the aminosulfonic, aminocarboxylic or aminophosphonic acid in a R₈⁺-buffer; and
- (ii) isolating the desired 13,17-disubstituted derivative of formula II.

48 (Withdrawn). A method for the preparation of compounds of formula II in claim 7 wherein R₁ and R₄ are each a group -NH-(CH₂)_n-SO₃⁻R₈⁺; R₂ is -OCH₃; R₃ is acetyl; R₈⁺ is a monovalent cation; m is 1 and n is 1 to 10, which comprises:

- (i) coupling the corresponding M-bacteriopheophorbide of formula I wherein R₁ is OH with N-hydroxy-sulfosuccinimide (sulfo NHS) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC);
- (ii) reacting the resulting M-bacteriopheophorbide-17³-N-hydroxy-sulfosuccinimide ester with an excess of an aminosulfonic acid of the formula H₂N-(CH₂)_n-SO₃H in a R₈⁺-buffer, thus obtaining a compound of formula I having a sole negatively charged group at position 17;
- (iii) reacting the product of step (ii) with an excess of H₂N-(CH₂)_n-SO₃H in a R₈⁺-buffer; and

(iv) isolating the desired compound of formula II.

49 (Withdrawn). A method for the preparation of compounds of formula II in claim 7 wherein R₁ and R₄ are each a group -NH-(CH₂)_n-COO⁻R₈⁺; R₂ is -OCH₃; R₃ is acetyl; R₈⁺ is a monovalent cation; m is 1 and n is 1 to 10, which comprises:

(i) coupling the corresponding M-bacteriopheophorbide of formula I wherein R₁ is OH with N-hydroxy-sulfosuccinimide (sulfo NHS) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC);

(ii) reacting the resulting M-bacteriopheophorbide-17³-N-hydroxy-sulfosuccinimide ester with an excess of an aminocarboxylic acid of the formula H₂N-(CH₂)_n-COOH in a R₈⁺⁻ buffer, thus obtaining a compound of formula I having a sole negatively charged group at position 17;

(iii) reacting the product of step (ii) with an excess of H₂N-(CH₂)_n-COOH in a R₈⁺⁻ buffer; and (iv) isolating the desired compound of formula II.

50 (Withdrawn). A method for the preparation of compounds of formula II in claim 7 wherein R₁ and R₄ are each a group -NH-(CH₂)_n-PO₃²⁻ R₈⁺; R₂ is -OCH₃; R₃ is acetyl; R₈⁺ is a monovalent cation; m is 1 and n is 1 to 10, which comprises:

(i) coupling the corresponding M-bacteriopheophorbide of formula I wherein R₁ is OH with N-hydroxy-sulfosuccinimide

(sulfo NHS) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC);

(ii) reacting the resulting M-bacteriopheophorbide-17³-N-hydroxy-sulfosuccinimide ester with an excess of an aminophosphonic acid of the formula H₂N-(CH₂)_n-PO₃H₂ in a R₈⁺-buffer, thus obtaining a compound of formula I having a sole negatively charged group at position 17;

(iii) reacting the product of step (ii) with an excess of H₂N-(CH₂)_n-PO₃H₂ in a R₈⁺-buffer; and (iv) isolating the desired compound of formula II.